Synthese en eigenschappen van dithienothiazinen en dithienothiopyronen

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SUMMARY

This thesis deals with the synthesis and the properties of the dithienothiazine and thienobenzothiazine systems.
The preparation of these compounds were performed with the intention to develop a route to the thiophene analogs of the phenothiazines, a class of neuroleptic drugs.
In Chapter 1 the literature concerning some structure-activity relationships of the phenothiazines is surveyed. Hypotheses of a possible mode of action of these drugs are mentioned, especially concerning charge-transfer mechanisms and the role of radical-cations as the active form of the drug.
Chapter 2 deals with some unsuccesful attempts to prepare dithienothiazines and benzothienothiazines by sulphuration of a dithienylamide and a thienylphenylamide with sulphur. By hydrolysis of these amides the first unsubstituted N-arylthienylamine and 3,3'-dithienylamine were synthesized and here shown to be reasonable stable compounds. A route to the dithienothiazine system was developed by the use of an Ullmann type cyclization reaction as is described in Chapter 3. In this way the 8-acetyl-8H-dithieno[2,3-b:2',3'-e]-1,4-thiazine (34) was prepared. In order to obtain physiological active compounds, a side chain with three carbon atoms must be introduced at the thiazine nitrogen atom and at the end of this chain a tertiary aminogroup has to be present. By per-

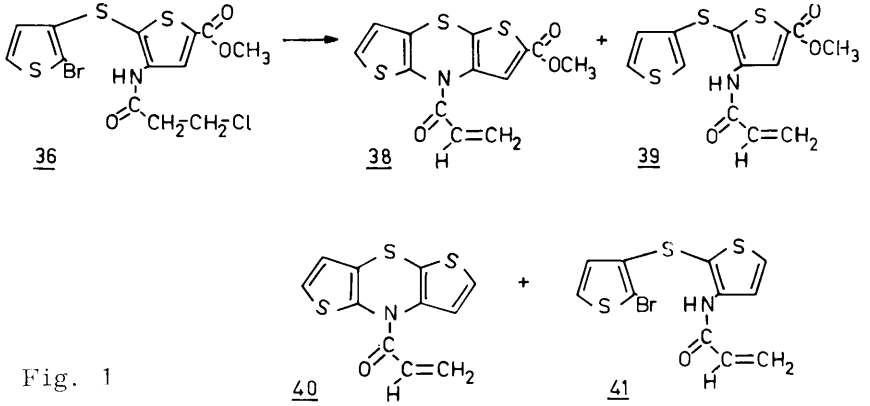
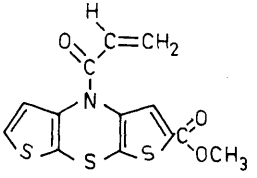


Fig. 1

forming the ringclosure reaction of compounds in which such a chain was potentially present four different products could be isolated. (Fig. 1)
The formation and the yield of these products depended strongly on the reaction conditions. By the same procedure the isomer (*46*) of *38* could be made as well as the thieno [3,2-b]benzo-1,4-thiazine (57) and the thieno [2,3-b]benzo-1,4-thiazine (58)



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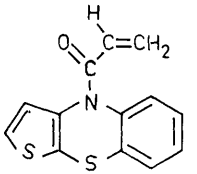

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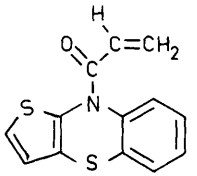

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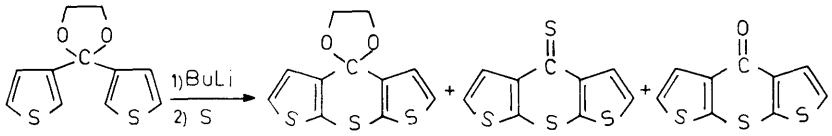
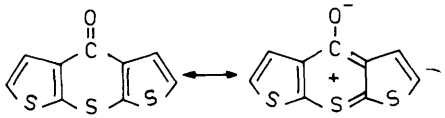
Chapter 4 deals with the synthesis of the N-methyl-piperazine derivatives of the thiazines *38*, *40*, *46*, *57* and *58* by a Michael addition; these derivates were isolated as their HCl salts.
The pharmacological screening for neuroleptic properties of the piperazine derivatives of *38*, *40* and *57* as their HCl salts is described in the addendum. These compounds were found to be inactive. A possible explanation of this lack of physiological activity is thought to be the influence of the amide function on the electron pair on the nitrogen, so that the formation of a radical-cation from this electron pair is hampered. This was checked by the electrochemical oxidations of these compounds where high values of the half-wave potentials were found for the first one-electron oxidation step.
Attempts to reduce the amide function were unsuccesful probably because the decomposition of the unsubstituted dithienothiazine nucleus via dithienothiazinium cations and radical-cations. Evidence for the easy formation of these cations is found in the massspectra of the dithienothiazine systems.
In Chapter 5 preliminary experiments are described to synthesize the analogs of the prothixenes: a class of neuroleptics related to the phenothiazines.

During the synthesis of the dithienothiopyrone system, which could be used as a starting material, an interesting reaction took place by lithiation and sulphuration of *77*, where the [2,3-b:3',2'-e]-8H-thiopyran-8-thione (80), the dithieno[2,-3-b:3',2'-e]-8H-thiopyran-8-one (81) and the ketal *79* were formed.

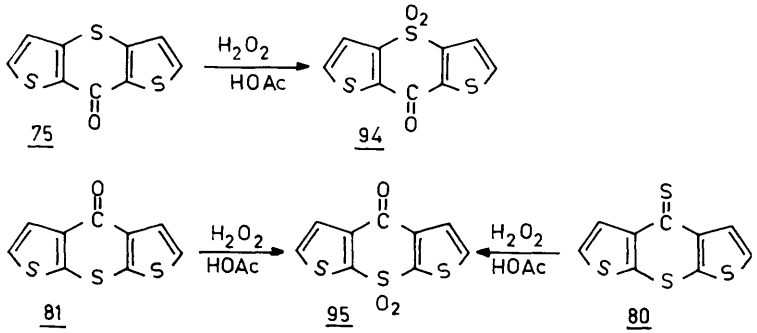


77 79 80 81

The dithienothiopyrone *81* lacks carbonyl activity, which can be traced to the existence of pseudoaromatic character.



An investigation of this behaviour in the compounds *80* and *81* together with the thiopyrone *75* was performed by UV and PMR spectroscopy. Carbonyl activity could be restored by oxidation of the compounds to the sulphones *94* and *95*.



75 94

81 95 80

In contrast to the thiopyrones *75* and *81* the sulphones did form oximes. The asymmetry, introduced by the oximidogroup

was demonstrated by the PMR spectra. A deshielding effect through space was noted for both α- and β-protons in the thiophene ring "syn" with respect to the hydroxyl group.